THREE AND FOUR TREATMENT CROSSOVER DESIGNS FOR ESTIMATING VARIOUS EFFECTS

by

Walter T. Federer
Biometrics Unit
337 Warren Hall
Cornell University
Ithaca, New York, 14853
U.S.A.

and

Ronald P. Kershner
Biometrics Department
Sterling-Winthrop Research Institute
Columbia Turnpike
Rensselaer, New York, 12144
U.S.A.

BU-775-M in the Mimeo Series of the Biometrics Unit, Cornell University.

Abstract

A study of a variety of two treatment p period crossover designs was reported earlier by the authors. In the present paper, three and four treatment p period crossover designs are studied. A number of designs have been described in published literature, but no comparison of their efficiency has been made. This is done herein using a criterion of efficiency involving the v-1 linearly independent contrasts among the v treatment effects. The crossover designs are of two basic types, i.e., when treatments do and do not precede themselves in a sequence. The designs are compared using direct effects, first order residual effects, and cumulative effects. For three treatments 3, 6, and 9 sequences and $3,4,\cdots,15$ periods were considered. For four treatments 4, 8, 12, and 16 sequences and $4,5,\cdots,20$ periods were studied. No one design was found to have uniformly best efficiency over all periods and sequences. Although patterns of efficiency of three and four treatment designs were generally the same, there were differences. This means that the efficiency of designs is not invariant with respect to number of periods, number of sequences, number of treatments, and type of design.

In addition to comparing efficiencies of various designs for direct, residual, and cumulative effects, the three treatment designs were studied to determine estimability of direct effect by first order residual effect interaction and cumulative effect by period interaction. There was only one of the designs which allowed estimation of the $(v-1)^2 = 4$ linearly independent contrasts among the $v^2 = 9$ direct by first order residual effect interaction terms. Three of the designs provided estimators of contrasts for the cumulative treatment effect by period interaction.

THREE AND FOUR TREATMENT CROSSOVER DESIGNS FOR ESTIMATING VARIOUS EFFECTS

1. Introduction

A variety of published designs provide efficient estimators of contrasts among direct and among residual treatment effects when the number of treatments exceeds two (see Kershner (1980) for a list of references). We consider the variance optimality and some estimability properties of the designs of Cochran et al. (1941), Williams (1949), Quenouille (1953), Lucas (1957), Linnerud, Gates and Donker (1962), Federer and Atkinson (1964), and Atkinson (1966) (see Table 1). Cochran et al. (1941) and Williams (1949) made use of orthogonal latin squares. The sequences were formed by placing the orthogonal latin squares side by side. Also, for v even it is possible to use a single square of v sequences and v periods which is balanced for one-period residual effects. The designs of Quenouille (1953) are of the following form for v = 3:

A	B	C	A	A	B	B	C	C
A	B	C	B	C	A	C	A	B
B	C	A	B	C	A	C	A	B
B	C	A	C	B	C	A	B	A
C	A	B	C	B	C	A	B	A
C	A	B	A	A	B	B	C	C

The designs of Lucas (1957) used a single latin square and then added another row duplicating the last row of the latin square. Linnerud et al. (1962) repeated the last row k times. The Federer and Atkinson (1964) designs used vt+1 periods and used the results from all periods or for omitting the first period; they used the CAC-W designs but added the extra v(t-1) + 1 periods. An example of their designs for v = 3, for 3 and 6 sequences, and 7 periods is:

Table 1

A Listing of Some Three and Four Treatment Crossover Designs

Class and Design		Abbreviated Notation	Literature Reference
CO(v,hv,v)	h=2,···,v-1, v odd h=1,···,v-1, v even	CAC-W	Cochran, Autrey, Cannon (1941) Williams (1949)
CO(v,hv,v+i),	i=1 or 2	L-L	Lucas (1957) Linnerud, et al. (1962)
CO(v,vj,vq+1),	j=1,···,v-1 q=1,2,3	FA	Federer (1955) Federer and Atkinson (1964)
CO(v,hv,kv),	k=2,3,···	A(k)	Atkinson (1966)
CO(v,v^2,2v)		QBP	Quenouille (1953) Berenblut (1964) Patterson (1973)

(See Kershner, 1980, and Kershner and Federer, 1981, for definitions and notations.)

A	B	C		A	B	C	A	B	C
B	C	A		B	C	A	C	A	B
C	A	B		C	A	B	B	C	A
A	B	C		A	B	C	A	B	C
C	A	B		C	A	B	B	C	A
B	C	A		B	C	A	C	A	B
A	B	C		A	B	C	A	B	C

The Atkinson (1966) designs were developed to reduce the variance of residual effects over the previous designs, leaving the variance of the direct effects in the FA and A(2) designs the same. An example of the latter design for $v = 3$, $k = 2$, $s = 3,6$, and $p = 7$ is:

A	B	C		A	B	C	A	B	C
A	B	C		A	B	C	A	B	C
B	C	A		B	C	A	C	A	B
B	C	A		B	C	A	C	A	B
C	A	B		C	A	B	B	C	A
C	A	B		C	A	B	B	C	A
A	B	C		A	B	C	A	B	C

With the exception of Cochran et al. (1941) and Williams (1949) designs, all the designs have the property that individual sampling units receive at least one of the treatments more than once. The designs of Quenouille (1953), Lucas (1957), Linnerud, et al. (1962) and Atkinson (1966) share the property that treatments precede themselves. Variance optimality of these designs for a varying number of periods is an unsolved problem in that criteria for variance optimality are for one set of effects, not several as encountered in crossover designs. It is addressed here for three and four treatment crossover designs. One comparison of the variance optimality of several classes of designs is given in Berenblut and Webb (1974), but these authors do not consider varying the number of periods,

sequences and amount of replication as is done here. An additional problem of ascertaining the estimability of contrasts among certain interaction effects is also considered.

For two treatments A and B, the criteria used for choosing efficient designs is based on minimizing the variance of differences of direct effects, $var(\tau_A-\tau_B)$, or the variance of differences of one period residual effects, $var(\rho_A-\rho_B)$. Such procedures are easily justified on the grounds that it is comparisons among the various treatment effects which are of primary interest. When the number of treatments is $v \geq 3$, there will be v-1 linearly independent (LIN) contrasts among the direct and among the residual treatment effects which need to be considered in comparisons of variance optimality. The measure of variance optimality adopted here is the determinant of the variance-covariance matrix of a set of v-1 LIN estimators of contrasts among the direct, among the residual effects, and among the cumulative treatment effects.

2. A General Formulation

Any linear model based on (3.1) of Kershner and Federer (1981) can be cast in matrix form as

$$\underset{\sim}{y} = \underset{\sim\sim}{X}\underset{\sim}{b} + \underset{\sim}{e} \qquad (2.1)$$

where $\underset{\sim}{y} = \{y_{ijk}\}$ is the lexicon-ordered nsp × 1 vector of observations, $\underset{\sim}{X}$ is a design matrix consisting of 0's and 1's of order nsp × q, $\underset{\sim}{b}$ is the q × 1 vector of population parameters, and the covariance structure is such that

$$var(\underset{\sim}{e}) = \underset{\sim}{V} = \underset{\sim p}{\Omega} * \underset{\sim ns}{I} = \sigma^2[(1-\rho)\underset{\sim p}{I} + \rho\underset{\sim p}{J}] * \underset{\sim ns}{I} , \qquad (2.2)$$

where * denotes a right Kronecker product.

Note that $\underset{\sim}{V}$ in (2.2) will be positive definite when $-1/(p-1) < \rho < 1$.

A set of generalized Aitken estimators of $\underset{\sim}{b}$ in (2.1) is given by

$$\underset{\sim}{b}^{0} = (\underset{\sim}{X}'\underset{\sim}{V}^{-1}\underset{\sim}{X})^{-}\underset{\sim}{X}'\underset{\sim}{V}^{-1}\underset{\sim}{y} \tag{2.3}$$

where $(\underset{\sim}{X}'\underset{\sim}{V}^{-1}\underset{\sim}{X})^{-}$ is a symmetric reflexive generalized inverse of $\underset{\sim}{X}'\underset{\sim}{V}^{-1}\underset{\sim}{X}$ satisfying

(i) $\underset{\sim}{X}'\underset{\sim}{V}^{-1}\underset{\sim}{X}(\underset{\sim}{X}'\underset{\sim}{V}^{-1}\underset{\sim}{X})^{-}\underset{\sim}{X}'\underset{\sim}{V}^{-1}\underset{\sim}{X} = \underset{\sim}{X}'\underset{\sim}{V}^{-1}\underset{\sim}{X}$,

(ii) $(\underset{\sim}{X}'\underset{\sim}{V}^{-1}\underset{\sim}{X})^{-}\underset{\sim}{X}'\underset{\sim}{V}^{-1}\underset{\sim}{X}(\underset{\sim}{X}'\underset{\sim}{V}^{-1}\underset{\sim}{X})^{-} = (\underset{\sim}{X}'\underset{\sim}{V}^{-1}\underset{\sim}{X})^{-}$,

(iii) $[(\underset{\sim}{X}'\underset{\sim}{V}^{-1}\underset{\sim}{X})^{-}]' = (\underset{\sim}{X}'\underset{\sim}{V}^{-1}\underset{\sim}{X})^{-}$.

The covariance matrix of $\underset{\sim}{b}^{0}$ in (2.3) is then

$$\mathrm{var}(\underset{\sim}{b}^{0}) = (\underset{\sim}{X}'\underset{\sim}{V}^{-1}\underset{\sim}{X})^{-} . \tag{2.4}$$

One set of v-1 LIN contrasts among, say, the direct effects can be of the form

$$\underset{\sim}{K}'\underset{\sim}{b} = \begin{bmatrix} \tau_1 - \tau_v \\ \tau_2 - \tau_v \\ \vdots \\ \tau_{v-1} - \tau_v \end{bmatrix} \tag{2.5}$$

Equivalently, one could consider a set of v-1 LIN contrasts among the residual effects such as

$$\underset{\sim}{L}'\underset{\sim}{b} = \begin{bmatrix} \rho_1 - \rho_v \\ \rho_2 - \rho_v \\ \vdots \\ \rho_{v-1} - \rho_v \end{bmatrix} . \tag{2.6}$$

In (2.5) $\underset{\sim}{K}'$ is a v-1 × q matrix of contrast coefficients having full row rank v-1. The BLUE of (2.5) is:

$$\underset{\sim}{K}'\underset{\sim}{b} = \underset{\sim}{K}'\underset{\sim}{b}^{0} = \underset{\sim}{K}'(\underset{\sim}{X}'\underset{\sim}{V}^{-1}\underset{\sim}{X})^{-}\underset{\sim}{X}'\underset{\sim}{V}^{-1}\underset{\sim}{y} \ , \tag{2.7}$$

which has a variance-covariance matrix of order v-1 given by

$$\text{var}(\underset{\sim}{K}'\underset{\sim}{b}^{0}) = \underset{\sim}{K}'(\underset{\sim}{X}'\underset{\sim}{V}^{-1}\underset{\sim}{X})^{-}\underset{\sim}{K} \ . \tag{2.8}$$

Berenblut and Webb (1974) use the criteria of D-optimality (e.g., Kiefer (1959)) to compare the variance optimality of certain designs. This procedure ranks designs on their ability to maximize $|\underset{\sim}{X}'\underset{\sim}{V}^{-1}\underset{\sim}{X}|$ or equivalently to minimize $|(\underset{\sim}{X}'\underset{\sim}{V}^{-1}\underset{\sim}{X})^{-1}|$. Although this procedure demands that $\underset{\sim}{X}$ in (2.1) be of full column rank, Berenblut and Webb note that ranking designs on the basis of this criteria is independent of the manner in which the model in (2.1) is reparameterized to yield a design matrix of full column rank.

The criteria of D-optimality is not used here. Instead the designs are compared on the basis of their ability to minimize the generalized variance in (2.8). By analogy with the two treatment case, this procedure is more intuitively appealing than D-optimality since often it is only the v-1 LIN contrasts among the various treatment effects which are of primary interest.

For use as a criterion of variance optimality three features of (2.8) are noted:

(i) $\underset{\sim}{X}$ can have less than full column rank,

(ii) $\underset{\sim}{K}'(\underset{\sim}{X}'\underset{\sim}{V}^{-1}\underset{\sim}{X})^{-}\underset{\sim}{K}$ is nonsingular, and

(iii) ranking the designs on the basis of (2.8) is independent of the choice of the particular form of the v-1 LIN contrasts generated by $\underset{\sim}{K}'$ in (2.5).

The development of these three features is given in Kershner (1980).

3. Variance Optimality with Respect to Contrasts Among Treatment Effects

Using the notation in the above section, several classes of crossover designs for three treatments are now compared on the basis of the variance optimality of estimators of contrasts among direct, first-order residual, and cumulative treatment effect, i.e.,

$$\min D = \min \left|\underset{\sim}{K}'\mathrm{var}(\underset{\sim}{b}^{0})\underset{\sim}{K}\right| = \left|\mathrm{var}\begin{bmatrix} \tau_1 - \tau_2 \\ \vdots \\ \tau_{v-1} - \tau_v \end{bmatrix}\right|, \qquad (3.1)$$

$$\min R = \min \left|\underset{\sim}{L}'\mathrm{var}(\underset{\sim}{b}^{0})\underset{\sim}{L}\right| = \left|\mathrm{var}\begin{bmatrix} \rho_1 - \rho_v \\ \vdots \\ \rho_{v-1} - \rho_v \end{bmatrix}\right|, \qquad (3.2)$$

and

$$\min C = \min \left|(K+L)'\mathrm{var}(b^{0})(K+L)\right| = \left|\mathrm{var}\begin{bmatrix} \tau_1 + \rho_1 - \tau_v - \rho_v \\ \vdots \\ \tau_{v-1} + \rho_{v-1} - \tau_v - \rho_v \end{bmatrix}\right|,$$

$$= \left|\mathrm{var}\begin{bmatrix} T_1 - T_v \\ \vdots \\ T_{v-1} - T_v \end{bmatrix}\right|, \qquad (3.3)$$

respectively.

For each of the designs listed in Table 1 the number of periods is varied from v to 5v and the number of sequences is taken to be 3, 6 or 9 for L-L, FA and A(k) while QBP is only defined for 9 sequences. Note that when s = 6 and p = 3, CAC-W, L-L, and FA are identical residual balanced orthogonal latin squares. The FA design is constructed according to Federer and Atkinson (1964). The A(k) designs are derived from the FA designs by repeating each row k times. The QBP design as originally constructed in Quenouille (1953) and Berenblut (1964) defined a $CO(v,v^2,2v)$. But here additional periods are added to define a $CO(v,v^2,5v)$. The design is replicated over the periods in such a way that periods $1,\cdots,2v$ define a QBP design as do periods $2v+1,\cdots 4v$; $4v+1,\cdots,6v$, etc. For L-L, FA and A(k), a nine sequence design is constructed by repeating one of the squares in the orthogonal set. In particular, the square defined by s = 1 in Federer and Atkinson (1964) is replicated. Tables 2, 3 and 4 show the values of (3.1), (3.2) and (3.3), respectively, for these designs. The values of the determinants in these tables are unique to within a multiple of $|\underset{\sim}{Q}|^2[\sigma^2(1-\rho)]^2$ where $\underset{\sim}{Q}$ is an arbitrary nonsingular matrix of order 2 as considered in $\underset{\sim\sim}{Q}\underset{\sim}{K}'\underset{\sim}{b} = \underset{\sim}{C}'\underset{\sim}{b}$. Note that since $\sigma^2(1-\rho)$ is a common factor, the relative ranking of the designs is invariant with respect to ρ. For all computations, a single observation in (2.1) is defined to have the expected value:

$$E(y_{ijk}) = \mu + \pi_i + \beta_j + \tau_t + \rho_r \,, \qquad (3.4)$$

where μ is a general mean effect, π_i is the effect of period i, $i=1,2,\cdots,p$, β_j is the effect of the j^{th} sequence, $j=1,2,\cdots,s$, τ_t is the direct effect of treatment t in the period in which it is applied, $t=1,2,\cdots,v$, and ρ_r is the carry-over or residual effect of treatment r in the first period after it was applied, $r=1,2,\cdots,v$.

On referring to Table 2, note that when the number of treatment sequences is three, A(2) minimizes the expression for D in (3.1) when $p = 3$ or 5 or $p \geq 9$. The FA design minimizes D when the number of treatment periods is 8, and, when the number of periods is four, L-L minimizes D. Note that when $p = 6$ or 7, the FA and A(2) designs provide equally efficient estimators of contrasts among direct effects.

The L-L and FA designs minimize D when $s = 6$ or 9 and $p = 3$ while for $s = 6$ or 9 and $p = 4$, L-L minimizes D. For $s = 6$ and $p \geq 5$, A(2) minimizes D and, for $s = 9$ and $p \geq 5$, QBP minimizes D.

The FA design tends to equalize the relative amount of within s.u. replication of direct and residual effects as the number of periods is increased. However, this property does not tend to make this design as efficient as the L-L design for $p = 4$ or 5 or the A(2) design when $p \geq 6$. The L-L and A(2) designs will generally be more efficient than FA since they have treatments preceding themselves in the sequences in addition to a varying degree of balance among direct and residual effects for a given number of treatment periods.

The A(3) design is inefficient for estimating contrasts among direct effects. When $p = 3$, contrasts among direct effects are not estimable for A(3) since they are completely confounded with contrasts among the sequence effects in (3.4). Design A(3) is a CR(3,3,3) when $p = 3$. Under a no-sequence-effects model and when ρ is sufficiently small (i.e., close to $-\frac{1}{2}$), A(3) will minimize D.

The values of R given in expression (3.2) are shown in Table 3. When $s = 3$ and $p \geq 8$, A(2) minimizes R. The A(3) design minimizes R when $s = 3$ and $p = 3$, and, for $p = 4$ and 5, L-L minimizes R. Note that when $s = 3$ and $p = 6$ or 7, the FA and A(2) designs are equally efficient. For the six or nine sequence designs,

Table 2

Values of Generalized Variance for a LIN Set
of Two Estimatable Contrasts Among Direct Effects

s	Type of Design	Number of Treatment Periods												
		3	4	5	6	7	8	9	10	11	12	13	14	15
		$\times 10^{-2}\sigma^2$					$\times 10^{-3}\sigma^2$							
3	L-L	833	40	27	-	-	-	-	-	-	-	-	-	-
	FA	833	53	42	14	10	85	69	63	47	36	30	27	24
	A(2)	133	42	21	14	10	90	49	43	28	26	20	19	15
	A(3)	-	75	33	31	13	11	10	63	60	57	33	31	30
		$\times 10^{-3}\sigma^2$												
6	L-L	130	53	44	-	-	-	-	-	-	-	-	-	-
	FA	130	83	57	34	26	21	15	13	11	9	8	7	6
	A(2)	284	99	34	28	18	16	11	10	7	6	5	5	4
	A(3)	-	176	81	74	25	23	22	13	12	12	8	7	7
		$\times 10^{-3}\sigma^2$					$\times 10^{-4}\sigma^2$							
9	L-L	69	25	21	-	-	-	-	-	-	-	-	-	-
	FA	69	44	27	15	12	92	69	58	48	39	34	30	25
	A(2)	13	44	16	13	82	75	49	44	31	28	22	21	17
	A(3)	-	79	36	33	12	10	10	58	56	55	34	33	32
	QBP	77	28	14	92	71	56	43	35	28	23	20	17	15

Table 3

Values of Generalized Variance for a LIN Set
of Two Estimable Contrasts Among Residual Effects

s	Type of Design	Number of Treatment Periods												
		3	4	5	6	7	8	9	10	11	12	13	14	15
		$\times 10^{-2}\sigma^2$						$\times 10^{-3}\sigma^2$						
3	L-L	2700	62	33	-	-	-	-	-	-	-	-	-	-
	FA	2700	83	64	22	14	11	90	76	57	43	35	31	27
	A(2)	1200	75	48	22	14	11	65	52	36	31	24	21	18
	A(3)	675	675	64	42	24	16	13	76	69	64	40	34	33
		$\times 10^{-2}\sigma^2$	$\times 10^{-3}\sigma^2$											
6	L-L	42	83	54	-	-	-	-	-	-	-	-	-	-
	FA	42	13	90	52	34	27	20	16	13	11	9	8	7
	A(2)	256	18	77	43	23	20	14	12	9	8	6	5	4
	A(3)	169	159	15	10	47	34	29	16	14	14	9	9	8
		$\times 10^{-3}\sigma^2$						$\times 10^{-4}\sigma^2$						
9	L-L	223	39	25	-	-	-	-	-	-	-	-	-	-
	FA	223	69	43	23	15	12	90	70	59	47	39	34	29
	A(2)	1156	79	36	20	11	90	64	53	40	34	26	24	20
	A(3)	750	71	69	46	21	15	13	70	65	61	42	38	36
	QBP	235	56	26	14	93	71	55	43	35	28	23	20	17

FA and L-L minimize R when $p = 3$ and, for $s = 6$ or 9 and $p = 4$ or 5, L-L minimizes R. When $s = 6$ and $p \geq 6$, A(2) minimizes R while for $s = 9$ and $p \geq 6$, QBP minimizes R.

Designs having the property that treatments precede themselves tend to be efficient for estimating contrasts among cumulative treatment effects (see Table 4). The A(3) design in particular is optimal with respect to minimizing C in (3.3) for $p \geq 8$ and for $s = 3$, 6 or 9. When $s = 3$, A(3) is uniformly optimal. The A(2) design is optimal when $s = 3$ and $p = 3$, 4 or 6. When $s = 3$ and $p = 5$, A(3) is optimal. When $s = 6$ or 9 and $p = 6$ or 7, A(2) is optimal for estimating contrasts among cumulative treatment effects. For $s = 6$ and $p = 3$, FA and L-L minimize C in (3.3) while for $s = 9$ and $p = 3$ QBP minimizes C. When $s = 6$ or 9 and $p = 4$ or 5 L-L minimizes C.

Many times in experimental work the total sample size rather than the actual number of sequences might be fixed, e.g., by cost considerations. When this is the case, one may want to compare the variance optimality of various designs for a fixed number of sampling units (s.u.'s). In this case, several s.u.'s are randomly assigned to each of the sequences in the design. For example, if 18k s.u.'s are available, where $k = 1,2,3,\cdots$, one might want to compare 3k replications of the six sequence designs such as FA, L-L or A(k) with 2k replications of the nine sequence QBP design for a varying number of periods. This is done in Table 5. The results tend to reinforce the optimality properties noted previously. When $p = 3$, FA and L-L are variance optimal for estimating contrasts among direct, residual and cumulative treatment effects. When $p = 4$, L-L is variance optimal with respect to estimating contrasts among direct effects, and it is optimal for residual effects when $p = 4$ or 5. The QBP design is optimal for residual effects when $p \geq 6$. The A(3) design is the optimal design for estimating contrasts among cumulative treatment effects when $p \geq 4$.

Table 4

Values of Generalized Variance for a LIN Set of Two Estimable Contrasts Among Cumulative Treatment Effects

s	Type of Design	Number of Treatment Periods												
		3	4	5	6	7	8	9	10	11	12	13	14	15
			$\times 10^{-1}\sigma^2$	$\times 10^{-2}\sigma^2$										
3	L-L	133	20	87	-	-	-	-	-	-	-	-	-	-
	FA	133	56	47	16	10	86	69	61	46	34	29	26	22
	A(2)	40	12	96	29	28	18	14	9	8	5	5	4	4
	A(3)	-	19	71	31	27	12	8	8	6	5	4	4	3
		$\times 10^{-2}\sigma^2$									$\times 10^{-3}\sigma^2$			
6	L-L	208	27	14	-	-	-	-	-	-	-	-	-	-
	FA	208	88	64	36	26	21	15	12	10	85	72	63	54
	A(2)	859	28	15	56	48	34	32	22	19	14	13	10	10
	A(3)	-	441	171	74	53	26	17	16	12	10	10	8	7
		$\times 10^{-2}\sigma 2$					$\times 10^{-3}\sigma^2$							
9	L-L	110	73	66	-	-	-	-	-	-	-	-	-	-
	FA	110	47	30	16	12	93	69	56	47	38	32	28	24
	A(2)	388	12	72	26	22	16	14	10	9	6	6	5	4
	A(3)	-	197	77	33	24	12	8	7	6	5	5	4	3
	QBP	94	21	87	46	33	26	20	16	13	10	9	8	7

Table 5

Values of Generalized Variance for Contrasts Among Direct, Residual, and Cumulative Effects for Fixed Sample Size

Type	s	Design	Number of Treatment Periods												
			3	4	5	6	7	8	9	10	11	12	13	14	15
			$\times 10^{-4}\sigma^2$									$\times 10^{-5}\sigma^2$			
Direct	6	L-L	144	59	49	-	-	-	-	-	-	-	-	-	-
	6	FA	144	93	63	38	29	23	17	14	12	98	85	74	63
	6	A(2)	316	110	38	31	20	18	12	11	78	70	56	53	42
	6	A(3)	-	196	90	82	28	26	25	14	14	13	86	82	79
	9	QBP	192	71	36	23	18	14	11	87	70	58	50	44	38
			$\times 10^{-4}\sigma^2$										$\times 10^{-5}\sigma^2$		
Residual	6	L-L	469	93	60	-	-	-	-	-	-	-	-	-	-
	6	FA	469	144	100	58	38	30	22	17	15	12	98	86	73
	6	A(2)	284	196	85	48	26	22	16	13	10	85	65	59	49
	6	A(3)	188	176	172	113	52	37	32	17	16	15	10	10	90
	9	QBP	588	139	64	36	23	18	14	11	86	70	58	50	43
			$\times 10^{-3}\sigma^2$									$\times 10^{-4}\sigma^2$			
Cumulative	6	L-L	231	30	16	-	-	-	-	-	-	-	-	-	-
	6	FA	231	98	71	40	29	23	17	14	12	94	80	70	60
	6	A(2)	955	31	17	62	54	38	35	24	21	15	14	11	11
	6	A(3)	-	219	86	37	27	13	8	8	6	5	5	4	3
	9	QBP	235	52	22	12	82	65	51	40	32	26	22	19	16

4. Direct-by-First Order Residual Treatment Interaction

A linear model having direct, residual and direct-by-residual treatment interaction is given by:

$$E(y_{ijk}) = \mu + \pi_i + \beta_j + \tau_t + \rho_r + \tau\rho_{tr} \quad , \tag{4.1}$$

where $\tau\rho_{tr}$ is an interaction effect of t^{th} direct and r^{th} one period residual effect and the other effects are as defined for (3.4).

Four linearly independent contrasts among the $\tau\rho_{tr}$ terms in (4.1) which jointly define direct by residual interaction can be defined as:

$$\theta_{AA,BB} = \tau\rho_{AA} - \tau\rho_{AB} - \tau\rho_{BA} + \tau\rho_{BB} \quad , \tag{4.2}$$

$$\theta_{AB,BC} = \tau\rho_{AB} - \tau\rho_{AC} - \tau\rho_{BB} + \tau\rho_{BC} \quad , \tag{4.3}$$

$$\theta_{BA,CB} = \tau\rho_{BA} - \tau\rho_{BB} - \tau\rho_{CA} + \tau\rho_{CB} \quad , \tag{4.4}$$

and

$$\theta_{BB,CC} = \tau\rho_{BB} - \tau\rho_{BC} - \tau\rho_{CB} + \tau\rho_{CC} \quad . \tag{4.5}$$

Any other contrast or any other LIN set of contrasts can be obtained as linear combinations of these. In order to estimate such a set of four LIN contrasts under model (4.1), it is necessary that treatments precede themselves in the sequences. If a linear model has m^{th} order residual effects, one will need to have treatments applied over m+1 successive periods. The QBP design is the only three treatment crossover design among those considered in this chapter, for which (4.2) - (4.5) are estimable under (4.1).

Since the treatments never precede themselves in the FA design, the

$\tau\rho_{ii}$, i=1,$\cdots$,v terms never appear so that no individual function in (4.2) - (4.5) is estimable. An estimable function which does not involve the $\tau\rho_{ii}$ terms in (4.1) is the difference between (4.3) and (4.4), i.e.,

$$\theta_{AB,BC} - \theta_{BA,CB} = \tau\rho_{AB} - \tau\rho_{AC} + \tau\rho_{BC} - \tau\rho_{BA} + \tau\rho_{CA} - \tau\rho_{CB} . \qquad (4.6)$$

The L-L and A(k) designs are modified versions of FA where one or more of the rows of the basic FA design is repeated. While the four simple contrasts in (4.2) - (4.5) are not estimable, one can construct a set of four LIN estimable functions involving differences of (4.2) - (4.5). One such set of LIN functions is:

$$\theta_{AA,BB} - \theta_{BB,CC} ,$$

$$\theta_{AB,BC} - \theta_{BA,CB} ,$$

$$\theta_{AA,BB} + 2\theta_{AB,BC} ,$$

and

$$\theta_{BB,CC} + 2\theta_{BA,CB} .$$

5. Cumulative Treatment-by-Period Interaction Effects

Treatment-by-period interaction effects for linear models having both direct and residual treatment effects are parameterized in terms of cumulative treatment by period interactions (CTPI) effects. This parameterization arises from considering models having both direct and residual effects and their corresponding interactions with periods.

Cumulative treatment effects (CT) are defined as the arithmetic sums of the direct and residual treatment effects. If contrasts among direct and residual effects are estimable, then so are the corresponding contrasts among CT with their

BLUEs being the sum of the corresponding BLUEs for direct and residual effects. Estimability of contrasts among direct and among residual effects ensures the estimability of the corresponding contrasts among CT. Such is not the case for CTPI. Designs which permit estimation of CTPI are characterized by the application of the same treatment to individual s.u.'s for k successive periods. The number of successive applications that are required for estimability is a function of the number of residual effects present in the model. Consider a model with m^{th} order residual effects. In order to estimate at least one contrast among CTPI within a minimum number of periods, the s.u.'s must receive m+2 successive applications of the same treatment as it takes m+1 periods for the cumulative effects to manifest themselves on the individual e.u.'s and at least one more treatment application is needed in order that the CT appear in at least two periods, thus defining a within-s.u. contrast among the CTPI. The successive applications of treatments causes part of the sequence to define a CR design. By using factorial theory, contrasts among CTPI can be constructed as in CR designs.

The model that is considered in this section is:

$$E(y_{ijk}) = \mu + \pi_i + \beta_j + \tau_t + \rho_r + \eta_{htr}\alpha\pi_{hi} \qquad (5.1)$$

where $\alpha\pi_{hi}$ defines the interaction between the h^{th} cumulative treatment effect and the i^{th} period effect and

$$\eta_{htr} \begin{cases} = 1 \quad \text{if} \quad h = t = r \\ \\ = 0, \text{ otherwise} \end{cases} .$$

The remaining effects in (5.1) are defined according to (3.4). Define a contrast among CTPI as:

$$\theta_{ij,i'j'} = \alpha\pi_{ij} - \alpha\pi_{ij'} - \alpha\pi_{i'j} + \alpha\pi_{i'j'} \qquad (5.2)$$

for $i,i' = 1,\cdots,v$, $i \neq i'$ and $j,j' = 1,\cdots,p$, $j \neq j'$. Contrasts among the interaction effects in (4.1) can be defined in terms of LIN θ's in (5.2) or LIN sets of linear combinations of the θ's.

The designs that provide estimators of contrasts among cumulative treatment-by-period interaction (CTPI) effects are L-L for $p = 5$, A(3) for $p \geq 6$ and QBP for $p \geq 2v$. Note that for CAC-W and FA, $\eta_{htr} = 0$ for every i and j so that contrasts among CTPI are not estimable under (5.1). For A(2), the contrasts among CTPI are completely confounded with sequences. The L-L design for three treatments has CTPI effects appearing only in periods four and five. For this design estimators of the θ's are:

$$\hat{\theta}_{A4,B5} = (-\bar{y}_{41\cdot} + \bar{y}_{51\cdot} + \bar{y}_{43\cdot} - \bar{y}_{53\cdot} + \bar{y}_{44\cdot} - \bar{y}_{54\cdot} - \bar{y}_{45\cdot} + \bar{y}_{55\cdot})/2 ,$$

$$\hat{\theta}_{A4,C5} = (-\bar{y}_{42\cdot} + \bar{y}_{52\cdot} + \bar{y}_{43\cdot} - \bar{y}_{53\cdot} + \bar{y}_{44\cdot} - \bar{y}_{54\cdot} - \bar{y}_{46\cdot} + \bar{y}_{56\cdot})/2 ,$$

and

$$\hat{\theta}_{B4,C5} = \hat{\theta}_{A4,C5} - \hat{\theta}_{A4,B5} = (\bar{y}_{41\cdot} - \bar{y}_{51\cdot} - \bar{y}_{42\cdot} + \bar{y}_{52\cdot} + \bar{y}_{45\cdot} - \bar{y}_{55\cdot} - \bar{y}_{46\cdot} + \bar{y}_{56\cdot})/2 .$$

The variance of each of these estimators is $2\sigma^2(1-\rho)/n$ where it is assumed that $k = 1,\cdots,n$ for every j. For an A(3) design, the estimable contrasts among CTPI are of the form:

$$\theta_{ij,i'j'} \text{ for } i,i' = A,B,C, \quad i \neq i' \qquad (5.3)$$
$$j = 2,5,8, \; j' = j+1 .$$

Other estimable functions can be obtained by taking suitable linear combinations of the contrasts defined by (5.2). The BLUEs of the θ's will be defined by linear combinations of those cell means where $\eta_{htr} = 1$. For example,

$$\theta_{A2,B3} = (\bar{y}_{21\cdot} + \bar{y}_{26\cdot} - \bar{y}_{22\cdot} - \bar{y}_{24\cdot} - \bar{y}_{31\cdot} - \bar{y}_{36\cdot} + \bar{y}_{32\cdot} + \bar{y}_{34\cdot})/2$$

with $\text{var}(\hat{\theta}_{A2,B3}) = \sigma^2(1-\rho)$. In general, $\text{var}(\hat{\theta}_{ij,i'j'}) = \sigma^2(1-\rho)$ where $\hat{\theta}_{ij,i'j'}$ is defined by (5.2). The total number of LIN estimable contrasts will be $(v-1)[v(k-1)-1]$. Note that a total of $(v-1)(kv-2)$ LIN contrasts would be estimable for a CR(v,v,kv) design. The remaining $2(v-1)^2$ CTPI contrasts which are not estimable for A(3) are completely confounded with contrasts among the sequence effects in (5.1).

For QBP, contrasts among CTPI are estimable under (5.1) only when $p > 2v+1$. Consider the QBP design for $v = 3$. To form a design with $p > 2v$ the additional periods can be obtained by repeating the basic design in such a way that periods $1,\cdots,2v$ are QBP as are period $2v+1,\cdots,4v$, etc. Certain contrasts among the CTPI will be estimable for the QBP design when $v = 3$ and $p > 2v+1$. For example, for $p = 8$, $\theta_{i2,j8}$, $i,j = A,B,C$ $i \neq j$ are estimable. When $p = 9$, additional estimable θ's are of the form $\theta_{i3,j9}$ and for $p = 10$, $\theta_{i4,j10}$. For each additional period after the 7^{th}, the estimable functions will be of the form $\theta_{ih,jk}$, $i,j = A,B,C$; $h = k-6$, $k = 8,9,\cdots$. For $p > 2v+1$ there are $(v-1)(p-2v+1)$ LIN estimable functions involving the CTPI effects in (5.1). The variance of estimators of each estimable $\theta_{ij,i'j'}$ is $2\sigma^2(1-\rho)$.

The A(3) design not only minimizes the variances of estimators of contrasts among CT, but it also minimizes the variances of estimators of contrasts among CTPI. In general, the efficiency of an A(k) design for estimating contrasts among CT and CTPI will improve with increasing k, but the disadvantage of doing so is that the number of treatment periods may become prohibitively large.

6. Some Four Treatment Crossover Designs

Variance optimality of the L-L, FA, QBP and A(k) designs for four treatments were assessed in terms of their ability of minimize the generalized variance of a set of estimators of three linearly independent (LIN) contrasts among the direct, first-order residual and cumulative treatment effects by using (3.1), (3.2) and (3.3), respectively. However, to save space, only the results for direct effects are given (Table 5). Those for residual and cumulative effects are given in Kershner (1980). The L-L, FA and A(k) designs are compared when the number of sequences is 4, 8, 12 and 16. The number of treatment periods is varied from four to twenty. The QBP design is only defined for sixteen sequences while the FA, A(k) and L-L designs can be constructed for any multiple of four sequences.

The FA design is constructed by using one or more designs from an orthogonal set of latin squares. As noted in Federer and Atkinson (1964), these designs are constructed for a varying number of periods and sequences by repeating orthogonal squares across the columns and down the rows of the design. The A(k) designs are obtained from the FA designs by repeating each treatment period k times. The L-L designs are obtained from an FA design having $p = 4$ by repeating the last period one or two times. Some additional designs having four sequences are considered here. These designs start with a balanced Williams (1949) design for

s = 4 and p = 4. This basic design is then repeated down the rows in order to define the appropriate number of treatment periods. These designs are denoted as L-L*, FA* and A(k)* in Table 6. Thus, for example, an L-L* design is a Williams (1949) design with the last period replicated one or two times while an L-L design uses one or more orthogonal latin squares rather than a Williams design.

Table 6 gives the generalized variance for direct effects as defined by (3.1). The single latin square design (L-L and FA) and the four sequence PBIB crossovers [A(2) and A(3)] do not perform well when compared to crossovers utilizing the Williams (1949) design; i.e., L-L*, FA*,A(2)* and A(3)*. Among the four sequence designs, the L-L* design is optimal for direct effects when p = 5 or 6. When p = 4, FA* and L-L* are variance optimal. It is interesting to note that FA* and L-L are equally efficient for direct effects when p = 5.

Among those designs utilizing the basic construction given in Federer and Atkinson (1964), the L-L design is variance optimal when p = 5 or 6. When s = 16, QBP is optimal for direct effects for p ≥ 6. As the number of treatment periods is varied from four to twenty, the FA* and A(2)* designs offer interesting comparisons. Note that A(2)* is more efficient than FA* when p = 7, 9, 11, 13, 15, 17, 19 and 20. When p = 18, these designs are equally efficient. The FA and A(2) designs do not have the same pattern. The A(2) design is more efficient than FA when p = 7 and 15. When p = 9, 17 and 19 these designs are equally efficient.

For residual effects, the four sequence designs based on Williams (1949) construction are uniformly more efficient for estimating contrasts among first-order residual effects than designs which use an unbalanced single latin square. Among the designs using the Federer and Atkinson (1964) construction, the FA and L-L designs are variance optimal for residual effects at p = 4 and s = 8, 12 or 16. When s = 4 and p = 4, A(2) is variance optimal. When p = 5 or 6, L-L is

Table 6

Values of the Generalized Variance for a LIN Set of Three Estimable Contrasts Among Direct Effects

s	Design	Number of Treatment Periods																
		4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
		$\times 10^{-3}\sigma^2$					$\times 10^{-4}\sigma^2$											
4	L-L*	83	36	28	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	FA*	83	58	33	24	11	95	66	55	36	31	24	21	16	14	11	10	8
	A(2)*	374	105	52	16	13	82	75	45	40	28	25	17	15	12	11	9	8
	A(3)*	844	250	216	51	36	32	11	10	94	54	52	50	29	27	26	18	17
	L-L	416	58	40	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	FA	416	217	39	27	11	95	67	45	33	26	21	17	14	12	10	9	7
	A(2)	76	73	47	21	17	95	85	46	41	28	25	17	15	12	11	9	8
	A(3)	-	62	58	46	34	32	14	13	12	60	58	56	29	28	27	18	17
		$\times 10^{-4}\sigma^2$					$\times 10^{-5}\sigma^2$											
8	L-L	135	50	38	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	FA	135	72	39	24	14	10	76	55	40	32	26	21	17	14	12	10	9
	A(2)	399	74	53	21	18	10	94	55	50	33	30	21	19	14	14	10	10
	A(3)	934	289	248	46	39	36	14	13	12	67	64	63	35	34	33	21	20
		$\times 10^{-4}\sigma^2$			$\times 10^{-5}\sigma^2$													
12	L-L	31	13	10	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	FA	31	18	11	65	40	29	22	16	12	10	8	6	5	4	4	3	3
	A(2)	100	20	15	59	50	29	26	16	15	10	9	6	6	4	4	3	3
	A(3)	233	73	64	13	11	10	40	37	35	19	18	18	10	10	10	6	6
		$\times 10^{-5}\sigma^2$					$\times 10^{-6}\sigma^2$											
16	L-L	138	58	44	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	FA	138	79	47	28	17	12	92	68	50	40	33	26	21	18	15	13	11
	A(2)	445	87	64	25	21	12	11	68	62	41	37	26	24	18	17	13	12
	A(3)	1040	324	280	55	47	44	17	16	15	81	78	75	44	42	41	26	25
	QBP	211	71	35	19	12	89	66	50	38	30	24	19	15	13	11	9	8

optimal for residual effects. Among the sixteen sequence designs, QBP is variance optimal for residual effects when $p \geq 7$. The A(2)* design is more efficient for residual effects that FA* when $p = 9, 11, 13,$ or 15 or when $p \geq 17$. The A(2) design is more efficient than FA for $p = 4$ or 7. When $p = 9, 17,$ or 19, A(2) and FA are equally efficient. Neither A(3) nor A(3)* are efficient designs for direct or residual effects, but these designs are variance optimal for estimating contrasts among cumulative treatment effects when the number of periods is sufficiently large.

The values of the generalized variance of contrasts among cumulative treatment effects are given by Kershner (1980). The A(3)* design is variance optimal for cumulative effects when $p \geq 9$ while for $s \geq 8$, A(3) is optimal when $p \geq 9$. When $s = 4$ and $p = 4$ or 5, L-L* is optimal for cumulative effects, and when $p = 6$, 7 or 8, A(2)* is optimal. When $s \geq 8$ and $p = 4, 6, 7$ or 8, A(2) is a variance optimal design for cumulative effects, and when $p = 5$, L-L* is optimal.

7. Discussion

As may be noted above, variance optimality of the type discussed here is not invariant with respect to type of design, number of sequences, number of periods, and number of treatments. Some designs have fairly good properties throughout the range of these variables. This means that an experimenter using a squential procedure for number of periods will have a dilemna in that the best design may depend upon the number of periods. In this case, it will be necessary to use the design which has relatively low variances for all periods.

The problem of measures of efficiency of designs taking into account some weighted function of direct, one-period residual, two-period residual, etc. effects still needs to be considered. We used the v-1 linearly independent contrasts

among v treatments for direct effects and for residual effects. Then, we used the same measure among direct plus residual equal cumulative effects. This gives equal weights to direct and residual effects which may not be appropriate in some situations.

Literature Cited

Atkinson, G. F. (1966). Designs for sequences of treatments with carry-over effects. Biometrics 22:292-309.

Berenblut, I. I. (1964). Change-over designs with complete balance for first residual effects. Biometrics 20:707-712.

Berenblut, I. I. and Webb, G. I. (1974). Experimental design in the presence of autocorrelated errors. Biometrika 61:427-437.

Cochran, W. G., Autrey, K. M. and Cannon, C. Y. (1941). A double change-over design for dairy cattle feeding experiments. Jour. Dairy Sci. 24:937-951.

Federer, W. T. (1955). Experimental Design: Theory and Application. Macmillan, New York.

Federer, W. T. and Atkinson, G. F. (1964). Tied double-change-over designs. Biometrics 20:168-181.

Kershner, R. P. (1980). On the theory of crossover designs with residual effects. Ph.D. Thesis, Cornell University, Ithaca, N. Y., May.

Kershner, R. P. and Federer, W. T. (1981). Two treatment crossover designs for estimating a variety of effects. Jour. Amer. Statist. Assoc. 76:612-619.

Kiefer, J. (1959). Optimum experimental designs (with discussion). Jour. Royal Statist. Soc., B, 21:272-319.

Linnerud, A. C., Gates, C. E. and Donker, J. D. (1962). Significance of carry over effects with extra period latin square change-over design. (Abstract) Jour. Dairy Sci. 45:675.

Lucas, H. L. (1957). Extra-period latin-square change-over design. Jour. Dairy Sci. 40:225-239.

Patterson, H. D. (1973). Quenouille's changeover designs. Biometrika 60:33-45.

Quenouille, M. H. (1953). The Design and Analysis of Experiments. Charles Griffin and Co., Ltd., London.

Williams, E. J. (1949). Experimental designs balanced for the estimation of residual effects of treatments. Australian Jour. Sci. Res. (A), 2:149-168.